AMENDMENTS TO THE DRAWINGS

Please replace Fig. 6 as filed with the Replacement Sheets for Fig. 6, which are attached as Exhibit 1.

REMARKS

Restriction Requirement:

In view of the election to prosecute Group I in this application, claims 17-55 have been cancelled without prejudice.

Drawing Objection:

The Examiner objected to Figure 6. In making the objection, the Examiner asserted that "Figure 6A is missing the gray lines referred to in the specification and Figure 6 is so blurred that it does not show what is supposed to be shown." (Paper No. 20060626 at 2).

With a view towards furthering prosecution, Replacement Sheets for Figure 6 are submitted as Exhibit 1. The Replacement Sheets are simply a better copy of Figure 6 as filed. Accordingly, no new matter has been introduced by the Replacement Sheets. Approval and entry of the Replacement Sheets are respectfully requested.

In view of the foregoing, it is respectfully submitted that the objection has been rendered moot and should be withdrawn.

Specification Objections:

The Examiner objected to the specification for various informalities. (Paper No. 20060626 at 3). With a view towards furthering prosecution, the specification has been amended to correct, *inter alia*, the informalities noted by the Examiner. No new matter has been introduced by the amendments. Approval and entry of the amendments respectfully is requested.

In view of the foregoing, it is respectfully submitted that the objection has been rendered moot and should be withdrawn.

§112, First Paragraph Rejections

1. Written Description

Claims 2, 4, 10-14, and 16 have been rejected under 35 U.S.C. §112, first paragraph, for lack of written description. (Paper No. 20060626 at 4-7). In making the rejection, the Examiner acknowledged that "[t]he disclosure provides the sequence of the polypeptide having SEQ ID NO:1" and provides *in haec verba* support for claims 2, 4, 10-14 and 16 "regarding the 80% identity." (*Id.* at 5-6). Nonetheless, the Examiner concluded that claims 2, 4, 10-14, and 16 "contain subject matter which was not described in specification ...." (*Id.* at 4). The rejection appears to be based on the following findings made by the Examiner:

- "[t]he disclosure contains no examples of polypeptides having sequences that have at least 80% identity to SEQ ID No.: 1." (*Id.* at 6);
- "[t]here is no disclosure of any polypeptides other than SEQ ID NO:1 and no examples of polypeptides at least 80% identical to SEQ ID NO:1" (*Id.*);
- "[t]he specification is devoid of any characteristics that would define which polypeptides at least 80% identical might have that would give them the same function as the polypeptide having SEQ ID NO:1" (*Id.*);
- "[t]here are also no assays presented that would permit one of skill in the art to determine which characteristics that would define which

polypeptides at least 80% identical might have that would give them the same function as the polypeptide having SEQ ID NO:1" (*Id.*);

- "[t]here is no way to predict which 20% of the sequence could be altered and still maintain the function of the parent polypeptide, that having SEQ ID NO:1. The structure to function relationship is not set forth at all ...." (*Id.* at 7).

For at least the reasons set forth below, the rejection is respectfully traversed.

The patent statute requires that the "specification shall contain a written description of the invention," set forth in "full, clear, concise and exact terms." 35 USC §112, first paragraph. This written description requirement is separate and distinct from the statutory enablement requirement. *In re Barker*, 559 F.2d 588, 593, 194 USPQ 470, 474 (CCPA 1977).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed subject matter, *i.e.*, that the inventor had possession of the claimed invention. *MOBA, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1320, 66 USPQ2d 1429, 1439 (Fed. Cir. 2003); *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989); *Fiers v Revel*, 984 F.2d 1164, 1170, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); and *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997).

Compliance with the written description requirement of the statute is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). During prosecution, the Examiner has the burden of establishing a *prima facie* case, by a preponderance of the evidence, as to why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention recited by the claims. *In re Wertheim*, 541 F.2d at 263, 191 USPQ at 97 and *Ex parte Chen*, 2002 WL 87963, *3 (unpublished) (BPAI 2002).

The PTO has promulgated guidelines to be followed by Examiners in the evaluation of patent applications for compliance with the written description requirement of 35 USC §112, first paragraph. These guidelines do not have the force of law, but are based on the PTO's understanding of binding legal authority in this area. *See* MPEP §2163, 8th Ed. (Feb. 2003 Rev. 1) at 2100-158.

Thus, legal precedent and the PTO's own internal rules require that an Examiner:

> read and analyze the specification for compliance with the written description requirement;
>
> determine what each claim means; and
>
> compare the scope of each claim to the description in the application to determine if the applicant has demonstrated possession of the claimed subject matter.

(*See Id.* at 2100-159-165; *In re Wertheim*, 541 F.2d at 262, 191 USPQ at 96-97; *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972); and *In re Morris*, 127 F.3d 1048, 1053-1054, 44 USPQ 1023, 1027 (Fed. Cir. 1997)).

An applicant may show possession of a claimed invention in many ways, including through disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that the applicant was in possession of the claimed invention as a whole. Vas-Cath, Inc. v. Muhurkar, 935 F.2d 1555, 1564-65, 19 USPQ2d 1111, 1117-18 (Fed. Cir. 1991).

In the absence of a proper *prima facie* case, an applicant who complies with the other statutory requirements is entitled to a patent. *See In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Initially, we respectfully note that the rejection is riddled with factual flaws. For example, the Examiner asserts in the rejection that "[t]here is no disclosure of any polypeptides other than SEQ ID NO:1 ..." (Paper No. 20060626 at 6.). This is incorrect. For example, in addition to SEQ ID NO:1, the specification unambiguously discloses an isolated polypeptide derived from the p62 nucleoporin, namely "p62(336-522)," in formula II. (*See, e.g.*, ¶¶13, 40, and SEQ ID NO:2). Moreover, the specification further identifies, *e.g.*, eighteen (18) additional p62 polypeptide fragments. (*See* Fig. 2A). In short, contrary to the express findings in the Office Action, the specification ***does*** provide disclosure of polypeptides other than SEQ ID NO:1.

The Examiner also asserts that "[t]here are also no assays presented that would permit one of skill in the art to determine which characteristics that would define which polypeptides at least 80% identical might have that would give them the same function as the polypeptide having SEQ ID NO:1 (*Id.*)" This too is incorrect. For example, the specification provides an assay for identifying the effects of any p62 fragment on RelA translocation. The specification specifically compares the effects of

SEQ ID NO:1 (p62(1-392)), SEQ ID NO:2 (p62(336-522)), and the full length p62 polypeptide in this assay and notes that over-expression of SEQ ID NO:1 "inhibits RelA-induced NF-KB activity" and inhibits translocation of NF-KB across a nuclear membrane. (*See, e.g.*, ¶¶38 and 138). Based on these data, one skilled in the art would know that an isolated polypeptide having an amino acid sequence that is at least 80% identical to SEQ ID NO.1 would behave in a similar manner in the RelA translocation assay. Indeed, the specification specifically counsels one to use "the methods disclosed herein" to identify polypeptides that are, *e.g.*, 80% identical to SEQ ID NO:1:

> When the result of a given substitution cannot be predicted with certainty, the derivatives may be readily assayed according to the methods disclosed herein to determine the presence or absence of the desired characteristics. (*See* ¶51).

In sum, it is respectfully submitted that the rejection is factually flawed. Accordingly, the rejection should be withdrawn for this reason alone.

Moreover, as noted above, the specification provides *in haec verba* support for claims 2, 4, 10-14, and 16. We also note that these claims are original claims and provide written description support for themselves. *See, e.g., In re Gardner*, 480 F.2d 879, 880, 178 USPQ 149, 149 (CCPA 1973); *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Still further, and as also noted above, the specification does provide structure-function relationships and assays for determining which structures have the described function, namely inhibition of RelA-induced NF-$_K$B activity and inhibition of the translocation of NF-$_K$B across a nuclear membrane. (*See, e.g.*, ¶¶38 and 138).

In view of the forgoing, it is respectfully submitted that the specification does provide a sufficient written description for claims 2, 4, 10-14, and 16. Accordingly, for this reason also the rejection should be withdrawn.

2. Enablement

Claims 1-16 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. (Paper No. 20060626 at 8-10). In making the rejection, the Examiner purported to carry out a *Wands* analysis and, as appears, dealt with each of the eight factors in a sentence or less. The Examiner then concluded that it was "inescapable" that undue experimentation would be required to practice the "instant invention." (*Id.* at 10).

Of particular note in the apparently hurried *Wands* analysis were the findings that:

(1) "the amount of guidance provided by the specification is zero since there is no disclosure as to which 20% of the polypeptide having SEQ ID No.: 1 could be changed while retaining the function of inhibition of the translocation of activated NF-KB across a nucleic [nuclear] membrane"; and

(2) "the nature of the invention is the disclosure of a body of research attempting to establish that p62(1-393) inhibits the translocation of activated NF-KB across a nucleic [nuclear] membrane with no indication as to the medical significance of that inhibition." (*Id.* at 9).

As is well settled, the specification must describe the claimed invention in sufficient detail to enable any person skilled in the relevant art to make and use the full

scope of the claimed invention without undue experimentation. *See* 35 USC §112, first paragraph ("The specification shall contain a written description of the invention, and of the manner and process of making and using it, ... to enable any person skilled in the art ... to make and use the same ....") and *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

Although not explicitly set forth in the statute, enablement may be found where some experimentation (even a considerable amount) is required, so long as the experimentation is not "undue." *Ex parte Forman*, 230 USPQ 546, 547 (BPAI 1986); *see also In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (J. Miller concurring) (CCPA 1977); and *In re Rainer*, 347 F.2d 574, 577, 146 USPQ 218, 220-221 (CCPA 1965). The Federal Circuit, adopting the analysis set forth in *Forman*, has enumerated several factors which may be considered in determining whether claims require that one skilled in the art perform undue experimentation in order to practice the claimed subject matter: breadth of the claims; predictability or unpredictability of the art; relative skill of those in the art; state of the prior art; nature of the invention; working examples; amount of guidance; and quantity of experimentation necessary. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors are merely illustrative, not mandatory; they provide a general framework for analysis. *Enzo Biochem v. Calgene Inc.*, 188 F.3d at 1371, 52 USPQ2d at 1136; *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991).

In fact, enablement may still be present when an application contains no working examples or when prophetic examples are used. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d at 1576-77, 224 USPQ at 414 ("Use of prophetic

examples, however, does not automatically make a patent non-enabling.") and *In re Strahilevitz*, 668 F.2d at 1232, 212 USPQ at 563 ("Nevertheless, as acknowledged by the board, examples are not required to satisfy section 112, first paragraph.").

The Examiner has the burden to set forth a *prima facie* case by establishing a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Initially, we note that the rejection focuses exclusively on the "at least 80% identical" phrase recited in some, but not all, of the rejected claims. Indeed, claims 1, 3, 5-9, and 15 do not recite this phrase. Thus, it is respectfully submitted that if any thing is "inescapable," it is that the rejection with respect to claims 1, 3, 5-9, and 15 cannot stand and should be withdrawn.

Next, we respectfully note that the rejection is factually flawed. For example, the Examiner asserts that "the nature of the invention is the disclosure of a body of research attempting to establish that p62(1-393) inhibits the translocation of activated NF-KB across a nucleic [nuclear] membrane *with no indication as to the medical significance of that inhibition*." [2/] (Paper No. 20060626 at 9). Putting aside the flawed premise of this conclusion, namely, that "medical significance" is the *sine qua non* of enablement, the specification unambiguously discloses at least one "medical significance" of the claimed polypeptides, namely regulation of the immune response and/or identifying agents that regulate immune responses.

> [T]he present study suggests that p62:TRAF-3 interactions may be a means by which p62 organizes a signaling complex at the nuclear pore and in which

[2/] Unless otherwise stated, emphasis is ours throughout this Response.

> p62 induces NF-KB activiation. In this regard, certain clinically important anti-inflammatory and immunosuppressive agents, such as acetylsalicylic acid and cyclosporin A, are believed to function by inhibiting steps required for nuclear translocation of the transcription factors NF-KB and NF-At, respectively. ***These considerations indicate that TRAF-3:p62 interactions provide a novel target for therapeutic agents that may regulate immune responses***. (*See* ¶150) (internal citations omitted).

The rejection also asserts that "the amount of guidance provided by the specification is *zero* since there is no disclosure as to which 20% of the polypeptide having SEQ ID No.: 1 could be changed while retaining the function of inhibition of the translocation of activated NF-KB across a nucleic [nuclear] membrane." (Paper No. 20060626 at 9). This too is in error. For example, the specification discloses numerous methods to obtain a polypeptide that is at least 80% identical to SEQ ID NO:1. (*See, e.g.*, ¶47 (computer modeling), ¶48 (substitution of one specific amino acid for another), ¶49 and Table A (conservative substitutions), and ¶50 (specific amino acid modifications, which are known to increase polypeptide stability)). And, the specification discloses how to take such modified polypeptides and assess their effects on inhibition of RelA-induced NF-$_K$B and inhibition of the translocation of NF-$_K$B across a nuclear membrane. (*See, e.g.*, ¶¶38 and 138).

The rejection also makes quick note that the amount of experimentation is large and that the specification is "devoid of any working examples of polypeptides that are at least 80% identical [to SEQ ID NO:1]." (Paper No. 20060626 at 9). It is well settled, however, that the *amount* of experimentation is not the proper focus of a *Wands* analysis. Rather, the focus is on whether the experimentation is *undue*. Given the

extensive disclosure in the specification of how to identify and make polypeptides that are "at least 80% identical" to SEQ ID NO:1 (*see, e.g.*, ¶¶47-53 and Table A), assays (*e.g.*, RelA translocation assay) for identifying common functional features, *i.e.*, inhibition of translocation of NF-kB across a nuclear membrane (*see, e.g.*, ¶138 and Fig. 4), and the Examiner's admission that the level of skill in the art was "very high" (Paper No. 20060626 at 9), it is respectfully submitted that a careful and thorough analysis of the specification leads to the reasoned conclusion that all rejected claims are enabled, particularly the claims that recite "at least 80% identical," namely, claims 2, 4, 10-14, and 16.

Thus, for the reasons set forth above, it is respectfully submitted that the rejection should be withdrawn.

§101 Rejection

Claims 1-16 have been rejected under 35 U.S.C. § 101 for lack of utility. (Paper No. 20060626 at 10-13). In making the rejection, the Examiner asserted that "the claimed invention is not supported by either a specific and substantial asserted utility or [a] well-established utility." (*Id.* at 10).

The patent statute requires that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, ..." 35 USC §101.

As is well settled, the question of utility stands or falls with what is ***claimed;*** it does not extend to unclaimed subject matter. *Carl Zeiss Stiftung v. Renshaw plc.*, 20 USPQ2d 1094, 1100-1101 (Fed. Cir. 1991) (district court's ruling of

invalidity of claim 3 based on lack of utility reversed in view of the district court's misinterpretation of the claimed invention) and MPEP §2107.02 I at 2100-37 (8th Ed. August 2001) ("The claimed invention is the focus of the assessment of whether an applicant has satisfied the utility requirement.").

To reject ***claims*** in an application under § 101, an Examiner must show an unrebutted *prima facie* case of lack of utility. *In re Gaubert*, 187 USPQ 664, 666 (CCPA 1975). The PTO's *prima facie* showing "***must***" contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the ***claimed*** invention is neither both specific and substantial nor well established; (2) support the factual findings relied upon in reaching the conclusion; and (3) evaluate ***all*** relevant evidence of record, including utilities taught in the closest prior art. MPEP §2107.02 IV at 2100-41; Revised Interim Utility Guidelines Training Materials, p. 9; and Revised Interim Utility Examination Guidelines 66 FR 1092, 1098 (January 5, 2001).

There is no *per se* rule for compliance with the statutory requirement of utility under 35 USC §101. The character and amount of evidence that must be provided by an applicant will vary depending upon what is ***claimed*** and whether the asserted utility appears to contradict established scientific principles and beliefs. *Ex parte Ferguson*, 117 USPQ 229, 231 (Bd. App. 1957); *In re Gazave*, 154 USPQ 92, 96 (CCPA 1967); and *In re Chilowsky*, 108 USPQ 321, 325 (CCPA 1956). The applicant does ***not*** have to provide evidence sufficient to establish an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 206 USPQ 881, 883-884 (CCPA 1980) (reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court observed that a rigorous correlation is not necessary

when the test is reasonably predictive of the response.). Rather, evidence of an asserted utility is sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is "***more likely than not true***." MPEP §2107.02 VII at 2100-43.

At bottom, the utility threshold is *not* high. The disclosure of a single specific and substantial utility is all that is required. *In re Fisher*, 421 F.3d 1365, 1370, 76 USPQ2d 1225 (Fed. Cir. 2005) ("The government agrees with Fisher that the utility threshold is not high.")

Here, the rejection appears to read into the claims a requirement that a "specific disease or condition" be treated. The claims are not directed to methods for treating a particular disease or condition. Indeed, the claims recite "isolated polypeptides" and "pharmaceutical compositions." Thus, the proper focus for the utility analysis is on the "polypeptides" and "pharmaceutical compositions" as claimed.

In this regard, we note that the specification discloses that the claimed "polypeptides" and "pharmaceutical compositions" are useful to "regulate immune responses."

> These considerations indicate that TRAF-3:p62 interactions provide a novel target for therapeutic agents that may regulate immune responses. (*See*, *e.g.*, ¶150).

Regulating the immune response is both a specific and substantial utility. Unlike the ESTs claimed in *Fisher*, which were said to have "useful biological properties," or to be useful as "gene probes" or as "chromosome markers," here the specification discloses that the claimed "polypeptides" and "pharmaceutical compositions" have use in regulating the immune response. Unlike the facts in *Fisher*,

here the asserted utilities are specific to the claimed "polypeptides" and "pharmaceutical compositions" (*i.e.*, the asserted utilities are specific to the disclosed function of inhibiting NF-$_K$B translocation). And finally, unlike in *Fisher*, there can be no dispute that regulating the immune response is a recognized, current, real-world benefit. Nothing more is required. For this reason alone, it is respectfully submitted that the rejection is in error and should be withdrawn.

We further note that Example 5 of the Revised Interim Utility Guidelines Training Materials may be instructive. (*See*, pp. 34-35). In Example 5, the claim recited "The isolated protein consisting of the amino acid sequence set forth in SEQ ID NO:1." The Example postulates that the hypothetical specification discloses that the claimed amino acid sequence binds to a protein X. Although the Example concludes that the claim should be rejected under §101 and §112, first paragraph, it observes that the conclusion would be different had it been disclosed that X correlates with "an increased risk of heart disease." (*Id.*, p. 35).

The present specification, which discloses that the claimed polypeptides "may regulate immune responses" is like the note to Example 5, suggesting that a rejection under §101 and §112, first paragraph should not stand when the claimed compound is tied to "heart disease." Like "heart disease" in Example 5 of the Training Materials, "regulation of immune responses" embraces a family of possible diseases. And, like "heart disease," "regulation of immune responses" is specific to the presently disclosed polypeptides, is a substantial use (*i.e.*, it is not a throw-away use), and has a clear benefit in its current form. For this reason also, it is respectfully submitted that the rejection should be withdrawn.

For the foregoing reasons, it is respectfully requested that the rejection be withdrawn.

§112, First Paragraph Rejection

Claims 1-16 also have been rejected under the how-to-use prong of 35 U.S.C. §112, first paragraph. (Paper No. 20060626 at 13). In making the rejection, the Examiner asserted that "the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility" and thus, "one skilled in the art would not know how to use the claimed invention." (*Id.*).

The patent statute requires, in relevant part, that "[t]he specification shall contain a written description of the invention and of the manner and process of making and using it, ..." 35 USC §112, first paragraph. To reject a claim under the enablement provision of §112, first paragraph based on lack of utility under §101, an Examiner must show an unrebutted *prima facie* case of lack of utility. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

In the absence of a proper *prima facie* case, an applicant who complies with the other statutory requirements is entitled to a patent. *See In re Oetiker*, 24 USPQ2d at 1444 and MPEP §2164.07 I.A. at 2100-185 ("A 35 USC §112, first paragraph, rejection should ***not*** be imposed or maintained unless an appropriate basis exists for imposing a rejection under §101.... In particular, the factual showing needed to impose a rejection under 35 USC §101 ***must*** be provided if a 35 USC §112, first paragraph, rejection is to be imposed on 'lack of utility' grounds.").

Because, as demonstrated above, the rejection under §101 has been rendered moot, the rejection under the how-to-use prong of §112, first paragraph cannot stand. Accordingly, withdrawal of this rejection, respectfully is requested.

For the reasons set forth above, entry of the amendments and the Replacement Sheets, withdrawal of all objections and rejections, and allowance of all claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box. 1450 Alexandria, VA 22313-1450, on December 28, 2006.

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Respectfully submitted,

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